MUSCLE CROSS-SECTIONAL AREA IS IMPROVED AND PHYSICAL FUNCTION IS MAINTAINED AFTER HOME-BASED EXERCISE IN MEN WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER UNDERGOING ANDROGEN DEPRIVATION THERAPY

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A thesis submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Master of Arts in the Department of Exercise and Sport Science (Exercise Physiology).

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ABSTRACT

Mohamdod Saber Alzer: Muscle Cross-Sectional Area is Improved and Physical Function is Maintained in Men with Metastatic Castration-Resistant Prostate Cancer Undergoing Androgen Deprivation Therapy
(Under the direction of [Erik Hanson])

Exercise has been shown to be beneficial in alleviating detriments from androgen deprivation therapy (ADT). However, little work has been done examining the effects on less resource-intensive exercise in progressive forms of prostate cancer (PCa). The purpose of this study was to evaluate the effects of a home-based exercise program on muscle cross sectional area and physical function in men with metastatic castration-resistant prostate cancer (mCRPC) undergoing ADT.

For mCRPC patients completing the intervention (n=14), VL CSA increased by 12.6% (pre: 8.7cm^2 ± 3.3, post: 9.8 ± 3.9, p=0.012, *d*= 0.32) with no change in MQ. Those who met the adherence threshold experienced greater hypertrophy (n=9; pre: 9.27cm^2 ± 3.1, post: 11.77cm^2 ± 4.0; *d*= 0.7). PF was maintained after exercise training. VL CSA was lower in mCRPC (9.12cm^2 + 3.15) relative to CON (36.55cm^2 ± 7.04, p<0.001, *d*=4.95). Results are encouraging, but more work is needed to extend generalizability of results.

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LIST OF ABBREVIATIONS

PCa	Prostate Cancer
ADT	Androgen Deprivation Therapy
mPCa	metastatic Prostate Cancer
mCRPC	metastatic Castration-Resistant Prostate Cancer
GnRH	Gonadotropin Releasing Hormone
QoL	Quality of Life
CSA	Cross-Sectional Area
MQ	Muscle Quality
RT	Resistance Training
PSA	Prostate Specific Antigen
ACSM	American College of Sports Medicine
HADS	Hospital Anxiety and Depression Scale
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FACIT	Functional Assessment of Chronic Illness Therapy
DEXA	Dual-Energy X-ray Absorptiometry
ADLs	Activities of Daily Living
SPPB	Short Physical Performance Battery
HRR	Heart Rate Reserve
VL	*Vastus Lateralis*

CHAPTER 1: INTRODUCTION

Prostate cancer

Prostate cancer (PCa) is the most commonly diagnosed and second most fatal cancer amongst men with approximately 165,000 diagnoses and 27,000 deaths occurring annually[1]. Although treatment advancements have been made, the number of incidences are still high relative to other forms of cancer[1]. The 5-year survival rate for localized PCa is >95%; however, metastatic prostate cancer (mPCa) has survival rates of ~30%, which varies based upon the location of metastasis and medications prescribed to those diagnosed[1–4].

PCa is a hormone-sensitive disease, with development and progression reliant on interactions between circulating androgen and androgen-cell receptors[5]. Those with localized PCa may undergo prostatectomy to remove the tumor, but are often prescribed androgen deprivation therapy (ADT) in the form of a gonadotrophin-releasing-hormone (GnRH) agonist to reduce the possibility of tumor proliferation after surgery[6]. ADT has previously been shown to effectively treat PCa by slowing the rate of disease progression, but PCa will likely (typically 2-3 years) progress into a hormone-insensitive phase[7–9] where the tumor independently upregulates androgen signaling[8,9]. Secondary forms of ADT are now often required (in conjunction with primary ADT via GnRH agonists) to induce a "super-castration" effect[3,5,10]. Men who reach this progression of the disease are clinically diagnosed with metastatic, castration-resistant prostate cancer (mCRPC)[3].

Although the additional ADT dosage increases survival by 4-5 months[11,12], side effects are further exacerbated relative to baseline ADT dosages, significantly decreasing muscle mass and physical function, increasing fatigue, and lowering overall QoL[13,14]. Individuals with mCRPC commonly become more sedentary, with disuse-atrophy further exacerbating symptoms of ADT[15,16]. Exercise training is one approach that helps counteract some of the negative side effects associated with ADT in less progressive forms of prostate cancer. However, far less is known regarding how exercise training affects physiological parameters in those diagnosed with mCRPC. This represents a key knowledge gap, as men with mCRPC face additional challenges due to additional forms of ADT.

ADT

ADT has been shown to be an effective anti-cancer treatment for PCa[4,17], comes in several different forms (e.g. Primary ADT such as GnRH agonists, Secondary ADT such as androgen receptor antagonists, and androgen synthesis inhibitors; see ADT section in Chapter 2), and is associated with numerous adverse side effects[16,18–20]. Those who are considered mCRPC face additional challenges due to the introduction of "super ADT" drugs, which further amplify androgen depletion[13,21]. Although the spread of cancer may be controlled, patients commonly experience muscular atrophy, as well as decreases to lean mass due to the effects of low testosterone. Following the initiation of super-castration (ADT + abiraterone), 4.3% of total body muscle mass was lost during the first 12 months, illustrating the severity of side effects[10]. Additionally, individuals undergoing super-castration levels of ADT have previously been shown to experience increases to sarcopenia, which in turn affects physical function[12,13,22]. Overall, this affects the ability to perform activities of daily living (ADLs)[23], suggesting the need to critically examine muscle variables as clinically relevant outcomes for this population.

Muscle Quality and Cross-sectional Area

Muscle size and quality are of particular interest in elderly populations and men with PCa on ADT due to their clinical significance[24,25]. Cross-sectional area (CSA) describes muscle size[26] and is a valuable physiological measurement due to its positive correlation with strength and function[27,28]. However, muscle atrophy (decreased CSA) occurs with aging and is a likely contributor to loss of force and the inability to perform ADLs effectively[29,30]. These decreases are of particular concern to those with mCRPC undergoing ADT, as the average age of an individual diagnosed with mCRPC is 74 years[31], suggesting that this population is already at risk for age-related declines in muscle mass which are accelerated by the use of ADT[18,32]. Additionally, aging affects other myogenic variables such as muscle quality (MQ)[28], which is a muscle's capacity to generate force per unit size[33]. Declines in strength are not strictly due to sarcopenia, but may be attributed to how aging affects MQ[34]. Changes to MQ may include a decrease to the number of contractile proteins or an increase in the amount of intramuscular triglycerides present[24,34], with the latter potentially maintaining the muscle size but not force. To our knowledge, only one study has examined MQ in men with PCa on ADT, in which participants experienced an 18.9% decrease after 20 weeks of treatment[35]. The combination of ADT and sedentary lifestyle behaviors suggests that those with mCRPC are prone to severe detriments to MQ and CSA, which are related to muscular strength and function. Ultimately, this affects overall QoL[30,36], emphasizing the need for therapeutic remedies to counteract these deleterious events[35]. Exercise interventions in particular have the potential to help to reverse the side effects of ADT.

Exercise in PCa

Exercise training, which may include combined RT and AE, is a powerful, complementary therapy for reducing ADT-related side effects[37–39], but the majority of reported benefits from exercise interventions regarding PCa patients on ADT do not specifically include those diagnosed with mCRPC[37,39–41]. Resistance training (RT) particularly has elicited improvements with minimal occurrences of adverse events in both localized and metastatic disease. While testosterone ablation is not conducive to maintaining muscle mass[10,25,40] our group has demonstrated that individuals with localized PCa undergoing ADT were able to experience increases in muscle protein synthesis[42] and muscle hypertrophy[39] and were similar to healthy men that also led to improvements to physical function, muscle endurance, and QoL[39]. RT trials involving metastatic PCa participants have been able to illustrate benefits as well, with improvements in physical function, activity levels, lean mass, and lower body strength[37,38]. Additionally, aerobic exercise has also shown to be beneficial by providing an unfavorable microenvironment for tumor development[43], and helps to improve cardiorespiratory fitness and self-reported physical function[44]. Overall, there is emerging evidence to suggest that exercise training can provide benefits for men with PCa on ADT. However, little is known regarding how exercise training may affect men with mCRPC, a group that is likely to have greater ADT-related side effects and disease burden.

To our knowledge, there are two preliminary exercise trials in men with mCRPC. In an initial report, men randomized to combined exercise training or usual care with men attempting 98% of the workouts and completing 78% as prescribed experienced no safety issues (Kenfield & Chan, unpublished data). Another single-arm home-based trial is currently underway but has yet to report study outcomes[46]. These ongoing trials, as well as the current study, used home-

based exercise training. While supervised trials provide the benefits of increased safety, motivation, and control, they are also resource intensive and require participants to live close to training facilitates (or be willing to travel). Home-based training reduces or removes many of these barriers, including access to equipment, travel, socioeconomic status, and functional deficits from maximal androgen blockade[47]. Recent studies have investigated the feasibility of home-based exercise trials during ADT for localized PCa[48,49]. One trial in particular indicated that home-based exercise training in men with localized PCa undergoing ADT demonstrated similar benefits to fitness and QoL relative to more resource-intensive methods[50]. Considering these outcomes and the challenges faced by individuals diagnosed with mCRPC, remote training programs may prove to be a more viable yet physiologically stimulating option. However, little is known regarding changes to specific muscle variables after home-based exercise trials and how this may affect physical function, especially in mCRPC. Therefore, the aim of this study was to analyze muscle CSA and MQ in mCRPC in order to provide researchers with meaningful information regarding how home-based exercise affects muscle physiology in this population. Additionally, CSA will be compared to a control population, in order to understand the magnitude of detriment in those diagnosed with mCRPC undergoing ADT.

Research Questions

1. How does muscle CSA in mCRPC on ADT compare with control populations?
2. Does a 12-week, home-based exercise intervention produce changes in muscle CSA and quality in men with mCRPC on ADT?
3. Do changes in muscle CSA and quality after a home-based exercise intervention correlate with changes in physical function?

Sensitivity Analysis

1. Adherence may confound the relationship between muscle cross-sectional area, muscle quality, and functionality If there is heterogeneity in improvements, we may need to stratify subjects relative to our threshold to adherence, which is 70% of completed sessions.

Hypotheses

1. A 12-week, home-based exercise intervention will increase *vastus lateralis* CSA and MQ
2. Changes in CSA and MQ will positively correlate with physical function
3. Muscle CSA will be significantly smaller in mCRPC compared to control.

Limitations

1. Adherence to the exercise program, the resistance training in particular, was self-report. The aerobic (walking) portions were verified using wearable activity monitors.
2. This was a single-arm study. The primary purpose of this study was to examine feasibility, and it was unclear if the intervention was even possible.
3. All tests were completed in a single testing day.
4. Length and type of ADT were recorded but not controlled for due to a limited sample size.

Delimitations

1. All subjects were asked to complete all tests in the same day and in the same order, to minimize burden and reduce variance.
2. Adherence will be confirmed through Garmin VivoSmart HR smart-watch technology and weekly calls to subjects.

Significance

The analysis of muscle CSA and quality after a home-based exercise protocol allowed researchers to better understand how these variables contribute to physical function in this population. If the results are found to be significant, and if subjects adhere above our threshold of 70% to the exercise protocol, health-care practitioners may suggest home-based exercise to mCRPC patients on ADT in order to provide a convenient solution to alleviate the negative side effects of severe testosterone depletion. Ultimately, the results will provide details of the mechanism regarding muscle physiology in this population and will provide guidance for future research

CHAPTER 2: REVIEW OF THE LITERATURE

Cancer

Cancer accounts for a large proportion of death in today's world, making research in this field of particular interest. Cancer survival rates have exponentially improved over the past decade due to advances in early detection and enhanced treatment options[51]. This indicates that diagnosed individuals are living longer with cancer[1]. These benefits, however, are accompanied with consequences. Cancer medications greatly increase patient perceived fatigue, sedentary behavior, and ultimately the likelihood of metabolic syndromes and cardiovascular disease[19,52,53]. Although cancer patients are living longer, QoL is severely impacted during this time period[7,10,54,55] . The number of cancer diagnoses are projected to grow by approximately 20% within the next decade as the current population ages,[56] suggesting that more people are experiencing longer, but more difficult lives. Cancer is clearly a pertinent issue in society, and guidelines are needed to help individuals live longer lives that are healthy and meaningful.

Prostate cancer

Approximately 1 in 9 men will be diagnosed with prostate cancer at some point in life, making it one of the most common cancers in the world; however, only 1 in 41 men will die of this disease[1]. Death rates for PCa have significantly declined over the past forty years due to the multiple treatment options that are available for PCa patients, including chemotherapy[57], radiation therapy[58], prostatectomy [2], and ADT[53,59]. However, many of the medications prescribed to PCa patients often lead to high levels of fatigue, due to the deleterious effects they have on the

body. Ultimately, this increases sedentary behavior, and leads to higher instances of cardiovascular disease, making overall health a critical issue when prescribed cancer medications[15,16].

As previously stated, localized PCa has a 5-year survival rate of almost 100%, due to the effectiveness of prostatectomy[2]; however, survival rates drop significantly to 30%[60] for those with mPCa as the disease has spread to bone structures[1]. Patients may be prescribed medications such as ADT that help to control development of the cancer but leave individuals with harsh side effects. In many cases, men are able to live longer, but at an extreme functional disadvantage[7,18,54].

ADT

ADT is an effective treatment solution for men with advanced prostate cancer. As prostate cancer progresses, clinicians prescribe ADT to help improve patient life expectancy[4]. It functions to block androgen and androgen-cell receptors, including those associated with testosterone[61]. The most common mechanism by which ADT functions is through GnRH agonists, which have been shown to have similar effectiveness to surgical castration; however, some patients experience testosterone surges, which may have negative consequences in the development of prostate cancer[62–64]. For individuals with advanced PCa, the disease will eventually progress despite the use of GnRH agonists, as prostate tumors begin to mutate and overexpress androgens and androgen receptors[65]. This categorizes individuals as having castrate-resistant prostate cancer, and ultimately lowers life expectancy and QoL[66]. Clinicians may detect this resistance to GnRH agonists through increases in prostate specific antigen (PSA): a biomarker that clinicians utilize as a potential indicator for the development of prostate cancer tumors[59,67,68]. The literature suggests that ADT is an effective remedy for patients with mPCa. Multiple studies have indicated ADT's effectiveness in minimizing PSA levels at a rapid

rate,[69,70] while also being a cost-effective solution[71]. However, the benefits of ADT do not come without consequences.

A large body of evidence suggests that those diagnosed with PCa on ADT have low QoL scores and suffer from functional deficits[18,72]. Although life expectancy can be increased, patients may find difficulty in having meaningful years. Studies have indicated that patients on ADT report worse health-related QoL measures as opposed to age-matched healthy controls and localized PCa subjects,[73] due to the harsh side effects associated with testosterone suppression[62]. The effects progress when subjects are exposed to "super-castration" drugs, such as abiraterone or enzalutamide. These drugs are commonly prescribed in conjunction with GnRH agonists and amplify negative side effects that subjects face. In fact, one study specifically found a significant loss in lean muscle mass after subjects started abiraterone therapy,[10] indicating even worse outcomes for PCa patients. Clearly, solutions are needed to help mitigate losses in lean mass associated with ADT.

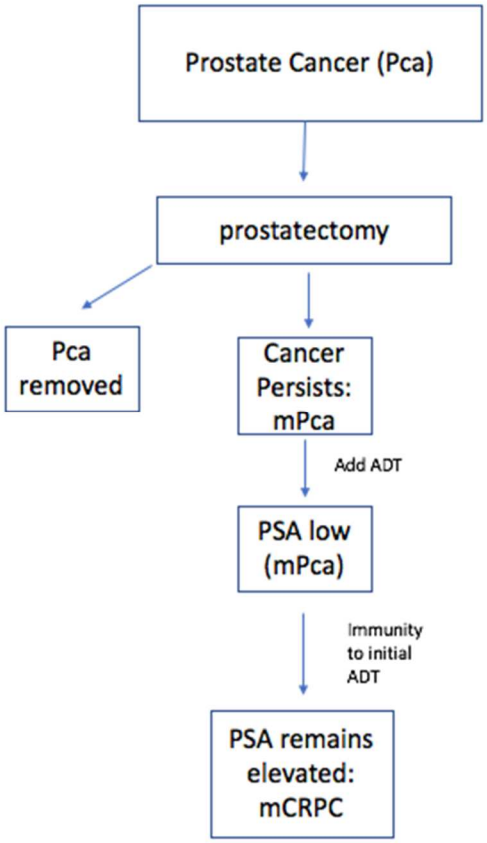

Figure 1. Process of diagnosis of metastatic castration-resistant prostate cancer (mCRPC). In some cases, prostatectomy is not required as clinicians are aware that the cancer has spread to bone structures (metastatic).

Exercise in Cancer Patients

A large body of scientific literature supports the idea that exercise has many benefits for cancer patients, including improved balance, lower risk of heart disease, lower risk of osteoporosis, lower risk of disease reoccurrence, and improved QoL[37,39,42,74–80]. Studies even suggest that exercise can help in the prevention of cancer as well, as lifestyle factors play a pivotal role in the development of the disease[81,82]. In fact, a recent analysis conducted by Moore et. al (2016) indicated that exercise is associated with a lower risk of contracting at least thirteen different cancers[83]. Although these results were more generalizable to individuals with higher BMIs, it can be implied that greater levels of muscle mass, strength, and an enhanced immune system may be beneficial in the prevention of cancer[84]. While healthy lifestyle factors may help prevent cancers, they can also help maintain strength and physical fitness during cancer treatments. A recent systematic review provided evidence that exercise can provide cancer patients with both CV and muscular fitness benefits, along with improvements to QoL[85]. The same review indicated that these exercises have been shown to be safe, with a low probability for adverse events. Clearly, exercise is beneficial for this population, with minimal risk for injury; however, conflicts exist that may make adherence to physical activity problematic.

Physical activity guidelines for cancer survivors set by the American College of Sports Medicine (ACSM) are in some ways ambiguous. For example, some of the RT recommendations state to "start with supervised program and progress slowly," but do not provide suggestions for exercise frequency or intensity. Also, many may have difficulties accessing a facility with staff who are qualified to work with at-risk popualtions[86]. Having ambiguous guidelines for this population may make adhering to a particular program difficult, and ultimately leads to less effective remedies for treating abnormalities that may accompany cancer survivors. Physical

activity barriers exist that limit cancer survivors from being able to exercise on a consistent basis[87–89]. Ultimately, these individuals have less accessibility to exercise, have less knowledge of various exercises to partake in, and have more limitations relative to other populations. Unfortunately, this is exacerbated in mCRPC patients, as they face a unique set of challenges due to the side effects of ADT.

Exercise in PCa

The negative side effects associated with ADT leave PCa patients with losses in lean mass, resulting in decreases to physical function and overall QoL[43]. Coupled with the adverse effects of sarcopenia, men of this population become extremely sedentary[90], resulting in an increased likelihood of contracting heart disease or diabetes mellitus[16,53,91]. Exercise has previously been researched as an advantageous tool for men of this population, as it may help to counteract harsh negative side effects (figure 2) exemplifies this mechanism[37,39,42]. Although multiple exercise regiments have been shown to be beneficial for PCa patients on ADT[37,39,43], no detailed exercise guidelines exist for this population. Perhaps physiological data from exercise interventions can give insight to policy makers on creating exercise guidelines for this population, ultimately helping to increase longevity and QoL.

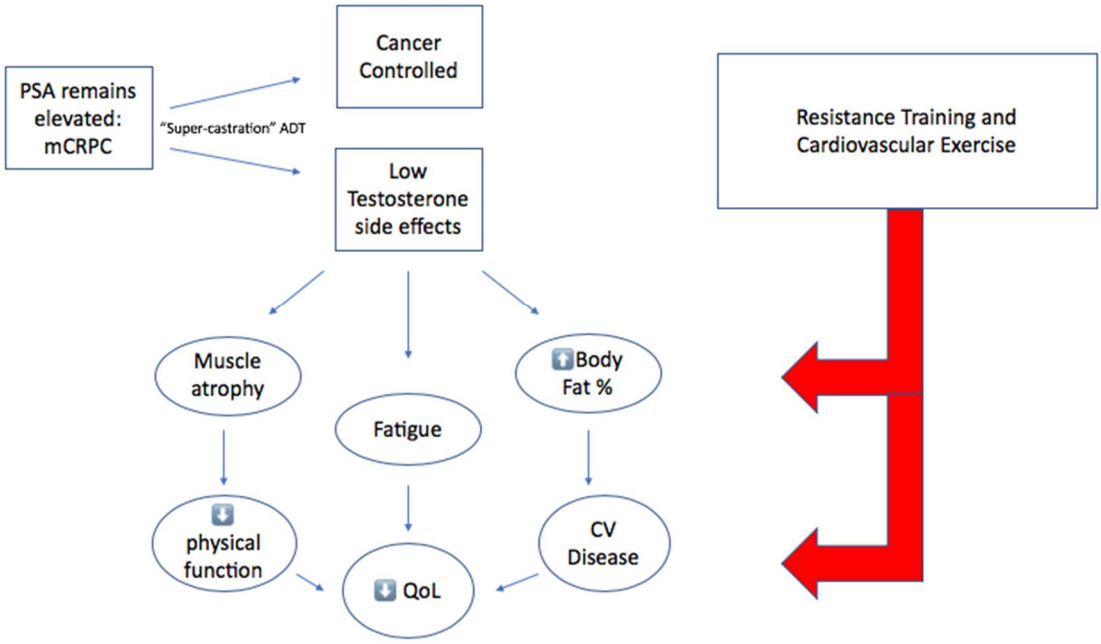

Figure 2. Mechanistic figure explaining exercise's role in mitigating negative ADT side effects.

A recent meta-analysis has suggested that though RT is beneficial for men with PCa on ADT, further research should be done to investigate particular protocols that may yield the best results while optimizing patient safety[92]. Multiple studies have investigated specific exercise programs for this population, and have illustrated that it can be beneficial to fighting ADT side effects[37–39]. In particular, Hanson et. al (2013)[39] found that a 12-week, supervised RT program for PCa patients receiving ADT significantly increased total body muscle mass by 2.7%, thigh muscle volume by 6.4%, power by 17%, and strength by 28%, suggesting that hypertrophy could occur even in the absence of testosterone. In addition to these physiological benefits, the same study found significant increases in patient physical function (20%), QoL (7%), and fatigue perception (38%). Another study by Galvao et. al (2018) [37] utilized a three-month, supervised program containing cardiovascular exercise, RT, and flexibility exercises. Results indicated that relative to sedentary subjects with the same disease, men on ADT who exercised experienced greater self-reported physical functioning and lower body muscle strength. The same study also

indicated that there were no exercise-related adverse events or skeletal fractures due to exercise, suggesting that the intervention was not only successful, but also safe. Undoubtedly, there are many benefits for PCa patients on ADT to reap from exercise; however, these programs need to be practical in order to increase adherence.

One suggestion to increasing exercise practicality for men on ADT is home-based exercise. Home-based exercise would allow individuals to exercise in a more comfortable environment, overcoming physical activity barriers that may persist due to socioeconomic status, lack of fitness facilities, or low physical functioning[48,89]. In addition, studies have reported that PCa patients may feel a level of embarrassment exercising at a facility and would also require staff members who are knowledgeable in working with at-risk populations[86]. Some studies suggest that home-based exercise can elicit positive outcomes to patient physiology and QoL[93], but the literature is scarce regarding PCa populations. Some studies suggest that home-based exercise is feasible for PCa subjects. Kim et. al (2018)[94] found an 80.4% 6-month exercise retention rate, and a 84.7% mean adherence rate for weight-bearing exercises. Beydoun et. al (2014)[15] found that men on ADT who exercised saw significant improvements to cardiorespiratory and strength fitness variables, with 97% of subjects planning to continue exercise after program completion; however, the researchers did not distinguish differences between home-based and supervised exercise protocols.

Previous literature has shown that home-based exercise can be feasible for prostate cancer populations, yet more research is needed to support this claim specifically for mCRPC. Men with PCa on ADT clearly suffer from lower QoL, and home-based exercise may be a way to provide an effective yet convenient solution. By assessing muscle cross-sectional area and volume, researchers will be able to assess important physiological variables that have been

previously associated with physical function and QoL. Health-care practitioners will be able to utilize this information by assessing these values in clinic and will hopefully obtain a greater understanding of patient well-being.

CHAPTER 3: METHODOLOGY

Design and Procedures:

Baseline and post-intervention testing occurred immediately prior to and after the 12-week home-based exercise intervention, respectively. Weekly phone calls were made throughout the duration of the intervention to assess subject adherence to the protocol and to address problems and questions subjects may have had about the intervention. Patient Reported Outcomes (PROs) were given to subjects prior to both baseline and post-intervention testing. Notes regarding exercise adherence and general well-being were recorded and reported to the primary investigator in order to address conflicts. Any questions regarding the exercise program were also addressed via weekly phone calls (Figure 3).

Subjects:

Inclusion criteria for this study included men with metastatic, castration resistant prostate cancer (mCRPC) on androgen deprivation therapy (ADT) who had testosterone levels less than 50ng/dL at the time of screening and had physician clearance to participate in moderate-to-vigorous exercise. Exclusion criteria included having greater than 90 minutes of exercise per week within six months of screening, current chemotherapy, and diagnosis of cardiorespiratory diseases limiting subjects from participating in exercise. After IRB-approval (#16-2427) was obtained, medical oncologists referred subjects to the study and referred individuals participated in an initial screening process. After an initial screening to confirm eligibility, a comprehensive medical history questionnaire was completed via telephone. The primary investigator reviewed the individual's completed medical history to confirm the subject was eligible and healthy

enough. After explaining testing procedures, all subjects provided IRB-approved written informed consent and HIPAA authorization forms prior to testing. An age- and BMI- matched control (CON) group was recruited as a sample of convenience.

Figure 3. Study Design

Patient Reported Outcomes:

Three questionnaires were used to assess PROs; these included the FACIT-Fatigue scale, the Hospital Anxiety and Depression Scale (HADS), and the Functional Assessment of Cancer Therapy-Prostate (FACT-P). The Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale was used to assess patient fatigue, and is known to have high internal validity (Cronblach's alpha = 0.96) and high test-retest reliability (ICC = 0.95) [95]. Scores range from 0-4, with higher scores corresponding to greater fatigue. The HADS questionnaire analyzes subject depression, and has been utilized as a valid questionnaire in research.[96] The score calculates ranges from 0-21, with higher scores translating to greater amounts of depression and anxiety. The FACT-P is a widely accepted questionnaire that assesses physical, emotional, and functional well-being, in addition to prostate-cancer related health issues. It also contains five functional scales, three symptom scales, and a QoL scale.

Body Composition

Body Composition was obtained through dual-energy x-ray absorptiometry (DEXA) scan (Discovery, Hologic, Marlborough, MA, USA). Total mass, lean mass, lean mass percentage, body fat percentage, bone mineral density, and bone mineral content were recorded. Upper body lean mass was calculated by adding lean mass values from the arms, trunk, and head. Lower body lean mass was calculated by adding the lean mass values from the legs. Appendicular lean mass was calculated by adding lean mass values from the arms and legs. All scans were completed by the primary investigator.

Muscle Ultrasound

Muscle cross-sectional area and echo intensity were obtained using ultrasound equipment (General Electric, Boston, MA, USA). Ultrasound measurements were taken from the mid-point of the greater trochanter of the femur and the lateral condyle of the tibia. Afterwards, cross-sectional analysis of the vastus lateralis muscle was obtained. Three-five images were taken, dependent upon the clarity of the image taken. Afterwards, cross-sectional area and uncorrected echo intensity was analyzed using ImageJ software (NIH, Bethesda, MD, USA). Echo intensity was corrected using techniques by Young et. al 2015. [97] Coefficient of Variations were calculated and reported between and within investigators in order to minimize error. The images were also blinded by the primary investigator before analysis by other members of the research team.

Physical Function Tests

Physical function tests were designed to capture the ability to perform activities of daily living (ADLs). A short physical performance battery (SPPB) score was calculated from the five chair stands, 2.44-meter usual walk, and three balance tests. These tests were used to address

physical function in similar populations, and allowed the research team to make comparisons accordingly[98]. Other tests included the 6-meter rapid walk, 2.44-meter usual walk, 8-foot timed up and go, three ten-second balance tests (including the semi-tandem, tandem, and neutral stances), five timed chair stands, timed stair-climb of ten steps, and a 400-meter walk. These tests were chosen due to their utilization in previous literature, allowing researchers to compare results to studies involving a similar population [39]. Subjects were familiarized with all physical function tests (excluding the 400 meter walk) by attempting one practice run, and thirty seconds of rest were given between each trial to minimize fatigue.

Exercise Intervention:

The 12-week home-based exercise intervention consisted of a subject-individualized aerobic component (walking) and an RT component using resistance bands (Hygenic corporation, Akron, Ohio, USA). Heart rate reserve (HRR) was calculated through cardiorespiratory testing done at baseline, and subjects were asked to walk at a specific HRR range week-by-week. The intervention was designed to progressively increase exercise frequency and volume, as advised by the Exercise Oncology Guidelines set by the American College of Sports Medicine[99]. The aerobic component intensity, duration, and frequency started as low as 40% of HRR for 15 minutes, one time per week (week 1) and ended as high as 65% of HRR for 30 minutes, 4 times per week (week 12). Retention rates were also calculated, with a target rate of 66%.

Exercise adherence was confirmed through the use of a Garmin VivoSmart HR smartwatch (Garmin, Olathe, KS, USA). This device was chosen due to its long battery life, cost, and ability for researchers to obtain HR and movement data remotely. Completion of cardiovascular exercise were confirmed if subjects had an elevated, steady HR in conjunction

with an increase in movement. Subjects were given resistance bands of four varying resistances (red, yellow, green, and blue) in order to promote intensity progression. Subjects were familiarized with upper body and lower body strength exercises. A member of the research team would show the subject the exercise and would ask them to repeat the exercise. The research team member would ensure that the exercise was completed correctly. The number of exercise sessions, sets, and repetitions varied weekly and in a graded fashion in order to promote strength gains amongst subjects. Subjects were then asked to record the time and day that exercises were completed in order for researchers to assess adherence. Subjects were compliant to an exercise session if 75% of the prescribed volume or exercises. Adherence was calculated by taking the number of attempted sessions, divided by the total number of sessions required multiplied by 100.

Statistical Analysis

Statistical analysis was completed using SPSS version 25 (SPSS, INC., Durham, NC, USA). An *a priori* value was set to $\alpha=0.05$ for tests of significance. All statistics were reported as mean (standard deviation). Changes in MQ, VL CSA, physical function and QoL with training were assessed using dependent samples t-tests. Participant characteristics (mCRPC vs. CON) were assessed using independent samples t-tests. A one-way between subjects ANOVA was performed to compare differences in muscle CSA between CON, mCRPC Pre and mCRPC Post. Pearson correlation coefficients were calculated between changes in CSA and changes in physical function tasks. Effect sizes were calculated using Cohen's *d* $(M_2-M_1)/SD_{pooled}$[100] with 0.2, 0.5, and 0.8 representing small, medium and large effects, respectively. Sensitivity analyses were conducted for individuals who meet or exceeded an adherence threshold of at least 70% of completed sessions, to explore if as differences may not be seen for those who did not comply to

the exercise intervention. One-sample t-tests relative to 75% were performed for individual RT exercises to determine if they were infeasible.

CHAPTER 4: RESULTS

Subject Recruitment

Sixty-two men with mCRPC on ADT were referred to this study. Of the sixty-two who were referred, 35.4% were eligible and decided to participate (n=22). (Figure 4).

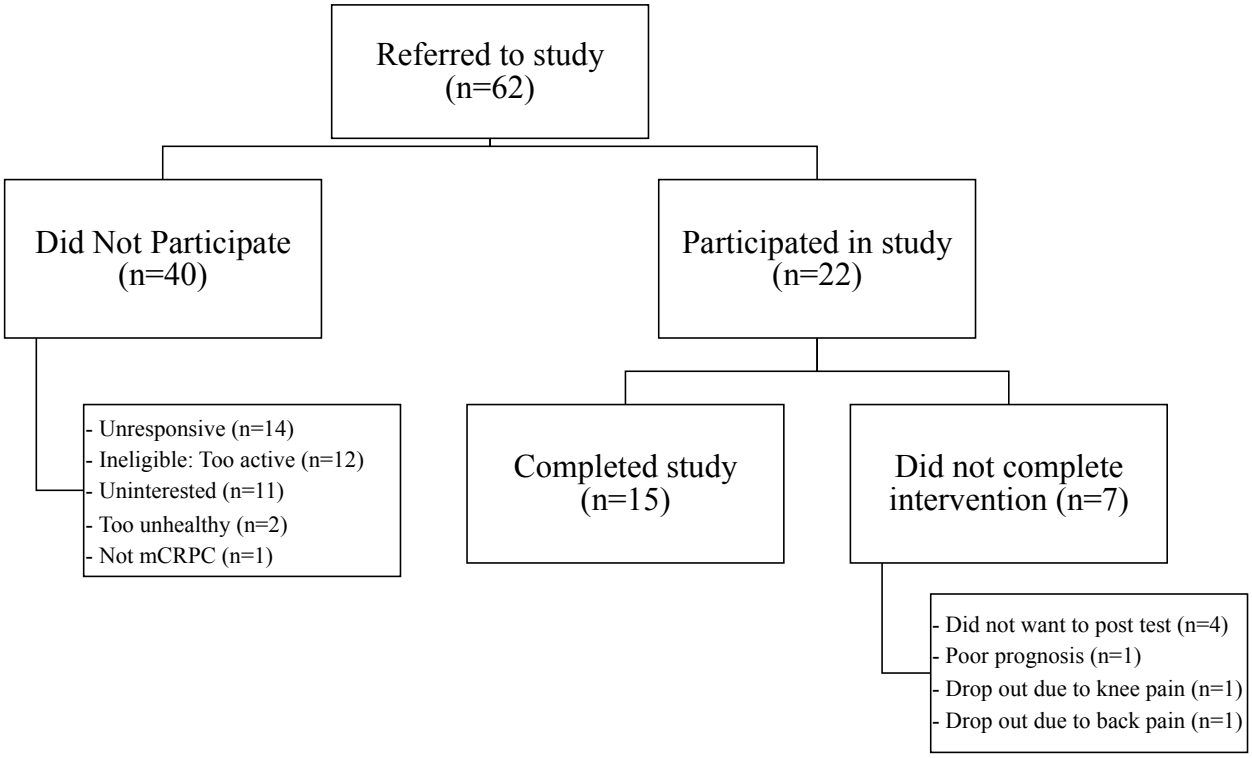

Figure 4. Consort diagram.

Descriptive Statistics

No significant differences were seen in descriptive variables between mCRPC and CON (Table 1). For the mCRPC group, all men were prescribed castrate-resistant ADT throughout the duration of the study. Information on other medications prescribed due to cancer diagnosis is also provided (Table 2).

Table 1. Participant characteristics between Metastatic, castration-resistant prostate cancer participants (mCRPC) (n=15) and Control (CON) (n=17)

	mCRPC	CON	p-value
Age (y)	72 (7)	69 (3)	0.650
Height (cm)	174 (8)	177 (7)	0.280
Mass (kg)	97 (21)	102 (9)	0.160
BMI (kg/m^2)	32 (7)	33 (2)	0.340

Mean (SD), BMI=body mass index. mCRPC= metastatic, castration resistant prostate cancer
CON= Control

Table 2. Cancer treatments for metastatic, castration-resistant prostate cancer (mCRPC) participants (n=15)	
Number on ADT	15
Duration of ADT (months)	36 (33)
Duration of CR ADT (months)	7 (5)
Type of ADT	
LHRHa, n(%)	1 (8)
Antiandrogen, n (%)	4 (28)
LHRHa + antiandrogen, n (%)	10 (65)
Previous Prostatectomy, n (%)	7 (46)
Previous Radiotherapy, n (%)	10 (65)
Previous Chemotherapy, n (%)	4 (26)
Time since chemotherapy (months)	13 (5)
Mean (SD), ADT = Androgen Deprivation Therapy, CR = Castrate-Resistant, LHRHa = Luteinizing-Hormone-Releasing-Hormone Agonist	

Retention and Adherence

Retention rates for the study was 68%, which met the target rate of 66%. The average total exercise adherence across the trial was 72.9% (23.3), with walking and resistance adherences at 80.1% (17.0) and 65.5% (29.5), respectively, which also met the targeted adherence of 75% (Figure 5). Adherence values for the exercise intervention were somewhat variable on a week to week basis (Figure 6), with the lowest average adherence for walking occurring at week 5 (68%) and for resistance training at week 10 raining (50%).

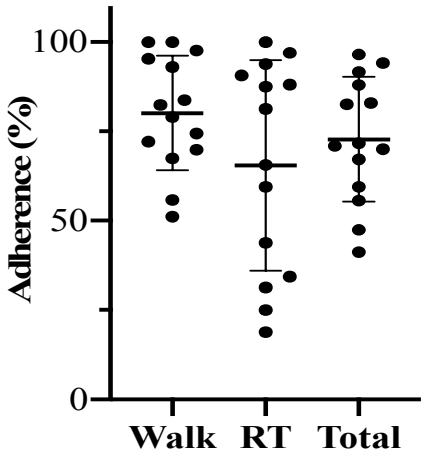

Figure 5. Summary of weekly adherence levels (individual exercises) for men who completed the intervention (n=14). Adherence is calculated for each week by dividing the number of sessions completed by the number of sessions prescribed by the research team.

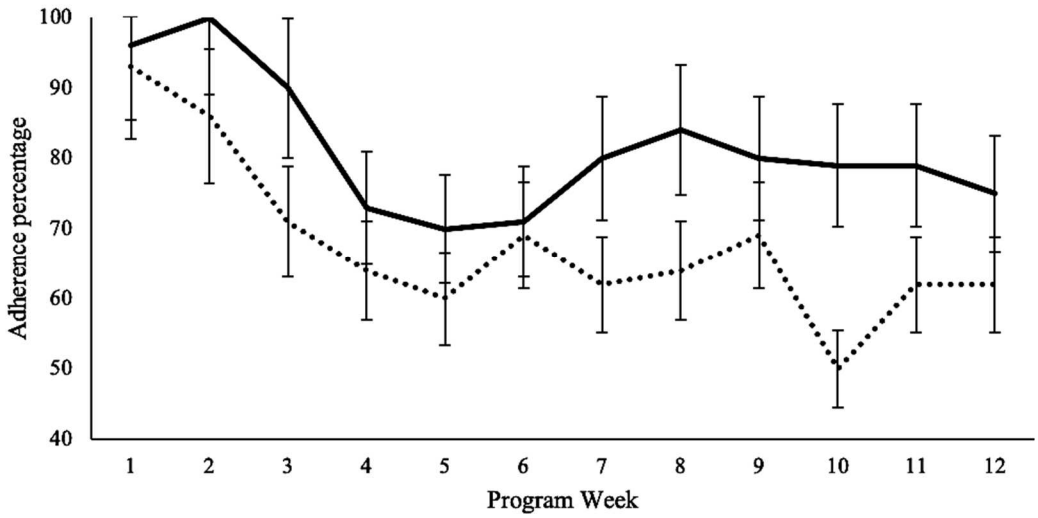

Figure 6. Summary of weekly adherence levels (bolded line walking, dotted line RT) for men who completed the intervention (n=14). Adherence is calculated for each week by dividing the number of sessions completed by the number of sessions prescribed by the research team. Data is reported as mean ± standard deviation.

The exercises that were significantly different relative to the target value (75%) were all of the floor abdominal exercises (all p<0.01, Figure 7) and push-ups (p=0.045).

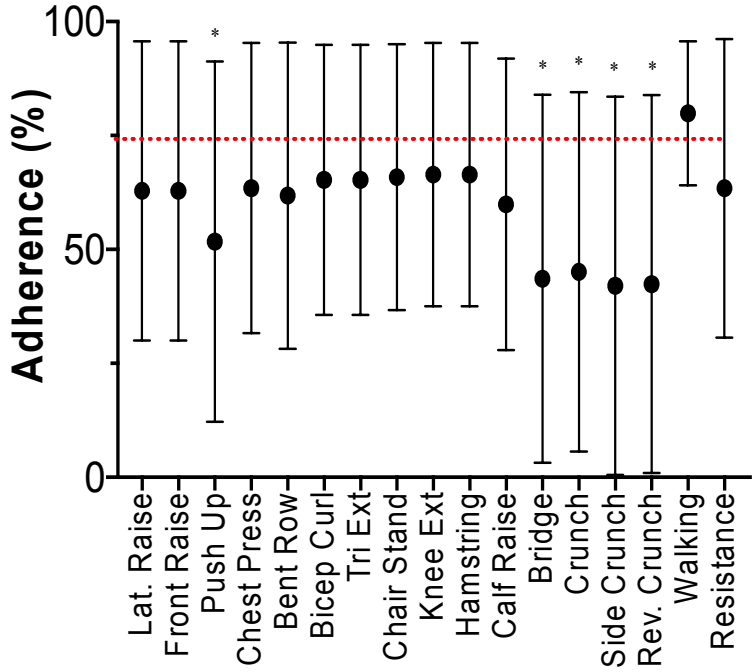

Figure 7. Exercise Adherence during the 12-week Home-based exercise intervention. Study adherence targets were 75% (red line). *p<0.05 vs. target value.

Vastus Lateralis CSA and MQ and Physical Function Tasks

Small to moderate increases in VL CSA were observed following the exercise intervention, with a 12.6% increase between baseline and post-intervention testing (p=0.012, *d* =0.32; Figure 8). Compared with controls (Average CSA 36.55 (6.02)), baseline VL CSA was 136% less (p<0.01, *d* = 5.75) and post-intervention was 127% less (p<0.01, *d* = 5.28). No differences occurred in VL MQ between pre and post-intervention testing (p=0.37, *d* = 0.22, Figure 9).

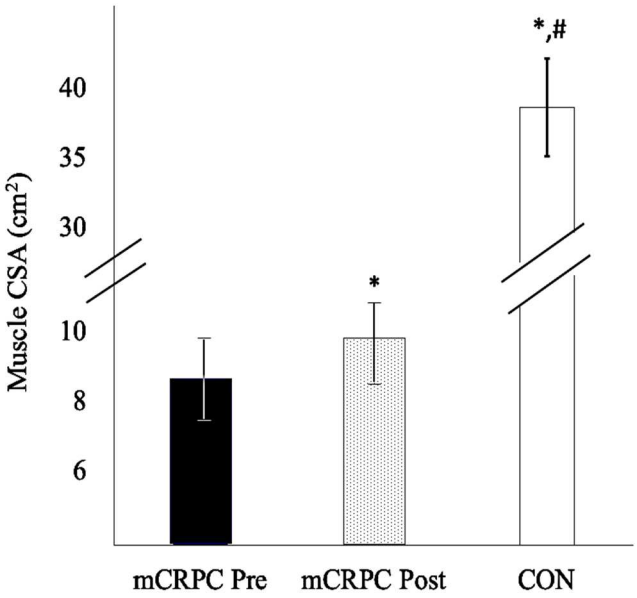

Figure 8. *Vastus lateralis* cross-sectional area **(**CSA) data for men who completed the 12-week home-based exercise intervention (n=14) compared to CON.

mCRPC = Metastatic, castration-resistant prostate

cancer, CON = Control

*p<0.05 compared to mCRPC Pre

# p<0.01compared to mCRPC Post

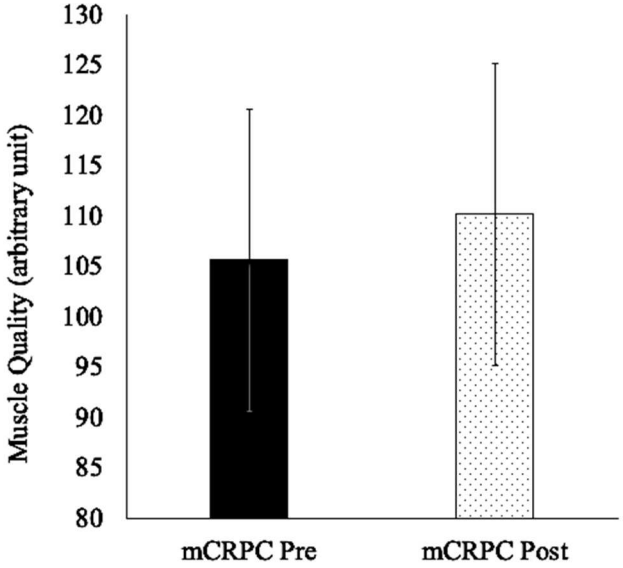

Figure 9. *Vastus Lateralis* Muscle Quality (MQ) data for men who completed the 12-week home-based exercise intervention (n=14).

mCRPC = Metastatic, castration-resistant prostate cancer

There were no changes in physical function in men with mCRPC who completed the intervention (Table 3).

Table 3. Summary of Results from *Vastus Lateralis* Cross-sectional area, *Vastus Lateralis* muscle quality, and Physical Function testing for men who completed the exercise intervention (n=14)

	Pre	**Post**	**p-value**	**Cohen's *d***
SPPB	10.5 (2.2)	11.0 (1.8)	0.130	0.28
5 Chair stands (sec)	13.1 (5.0)	12.4 (5.8)	0.210	0.14
6m Rapid Walk (sec)	4.5 (1.6)	4.6 (1.5)	0.380	0.08
8ft TUG (sec)	10.5 (11.1)	10.9 (11.3)	0.590	0.03
Stair Climb (sec)	6.5 (2.8)	6.3 (3.1)	0.250	0.08
400m walk (sec)	307.8 (127.0)	292.6 (116.8)	0.110	0.12

Mean (SD), VL = Vastus Lateralis, CSA = Cross-Sectional Area, MQ = Muscle Quality, SPPB = Short Physical Performance Battery, TUG = Timed-up and Go

Due to changes in VL CSA after the exercise intervention, correlation coefficients were determined to explore if greater changes in CSA correlates with changes in physical function tests. Beneficial relationships were observed between CSA changes and SPPB, 5 Chair stands, and 400m walk but these did not reach significance.

Table 4. Correlation Coefficient Table for changes in physical function tasks for men who completed the intervention. All Correlation Coefficients are compared to changes in *Vastus Lateralis* cross-sectional area for men who completed the exercise intervention (n=14)

Task	SPPB	Chair	6m Walk	TUG	Stair Climb	400m walk
Pearson's R	0.36	-0.32	0.20	0.20	-0.17	-0.33
p-value	0.19	0.24	0.47	0.47	0.54	0.22

SPPB = Short Physical Performance Battery, Chair = 5 Chair Stands, Rapid = 6m Rapid walk, TUG = 8' Timed-up and Go

Sensitivity Analysis

Due to heterogeneity in adherence levels, sensitivity analysis was required to examine how program adherence could affect the variables of interest. Of the fifteen men who completed the exercise intervention, nine completed the intervention with the desired adherence levels of at least 70% of completed exercise sessions. Men who completed the intervention and met the adherence threshold (n=9) had a 28.6% increase in muscle CSA between baseline testing and post-intervention testing (p=0.008, d = 0.70; Table 6). MQ did not change following training (p=0.50; d=0.27). In terms of physical function, maintenance was seen in all variables (Table 6).

Table 5. Sensitivity analysis for *Vastus Lateralis* cross-sectional area, *Vastus Lateralis* muscle quality, and physical function testing for men who had met the exercise adherence threshold of at least 70% for total adherence (n=9).

	Pre	Post	p-value	Cohen's *d*
VL CSA (cm^2)	9.2 (3.1)	11.7 (4.0)	***0.010***	0.70
VL MQ	109.1 (16.7)	113.4 (15.6)	0.500	0.27
SPPB	10.6 (1.9)	11.2 (1.4)	0.250	0.34
Chair Stand (sec)	10.1 (2.4)	9.8 (4.1)	0.490	0.11
6m Rapid Walk (sec)	4.6 (1.5)	4.6 (1.1)	0.960	0.01
8ft TUG (sec)	10.9 (11.9)	11.6 (14.6)	0.490	0.05
Stair Climb (sec)	6.5 (3.1)	6.5 (3.5)	0.950	0.01
400m Walk (sec)	335.4 (114.2)	321.8 (103.1)	0.370	0.12

Mean (SD), VL = Vastus Lateralis, CSA = Cross-Sectional Area, MQ = Muscle Quality, TUG = Timed-Up and Go

Correlation coefficients were calculated in order to understand the relationship between changes in CSA and changes in various physical function tests for men who completed the exercise intervention and met the adherence threshold.

Table 6. Correlation between changes in *Vastus Lateralis* cross-sectional area and physical function tasks for individuals who met our adherence threshold (n=9)

Task	SPPB	Chair	6m Walk	TUG	Stair Climb	400m walk
Pearson's R	0.30	-0.35	-0.25	0.28	-0.06	-0.14
p-value	0.43	0.36	0.52	0.46	0.88	0.72

SPPB = Short Physical Performance Battery, Chair = 5 Chair Stands, Rapid = 6m Rapid walk, TUG = 8' Timed-up and Go

CHAPTER 5: DISCUSSION

ADT is commonly prescribed during PCa to increase survival, but is accompanied by muscle atrophy and decreases in physical function and QoL[16,18–20,101]. Exercise training improves many of these outcomes in less progressive forms of PCa[37,39–41]. However, it is unknown if exercise improves body composition and physical function in advanced disease (e.g. mCRPC), particularly when looking at more sensitive and localized measures. Following a 12-week, home-based exercise intervention, VL MQ was unchanged while CSA increased by 12.6% following training. Greater adherence to training lead to greater improvements in CSA. Physical function was unchanged with training and was not associated with improvements in CSA. Preliminary data would suggest that exercise can induce increases to muscle size in this population, but that hypertrophy does not correspond with changes to physical function.

Limitations and Strengths

The current study had several limitations. The first was the lack of a control group. However, this was a feasibility trial and all participants were allocated to exercise because it was unknown if mCRPC would participate in home-based exercise to maximize the number of individuals that would potentially complete the intervention. Secondly, all testing was completed in the same day, which can increase subject fatigue during testing. However, subjects potentially had to travel great distances, and rest periods were incorporated. Thirdly, length and type of ADT affects the severity of side effects[10], but was not controlled for due to a limited sample size. Lastly, adherence values for the resistance training portion of the exercise intervention were self-

report and highly variable, but participants were contacted weekly, which improves home-based exercise adherence[102,103].

This study contained several strengths. This is the first trial to quantify differences in muscle CSA and MQ in mCRPC following training and compared to non-cancer controls and all scans were blinded to reduce analysis bias. The home-based approach likely helped to mitigate physical activity barriers. Although there was no dedicated familiarization session (Hanson 2016), subjects practiced all tasks prior to testing of functional tasks, which may have helped reduce error that may have occurred due to learning effects.

Key Findings

To our knowledge, this is the first study to examine the effects of exercise training on regional body composition and physical function in mCRPC undergoing ADT. This sample demonstrated localized muscle hypertrophy with no changes to MQ following exercise (Figure 8 and 9). Of note, VL CSA was ~4x smaller than an age- and BMI-matched control group, but training appeared reverse ADT side effect (Figure 8, d=0.32), with greater adherence leading to additional benefits (Table 6, d= 0.7). Although improvements in regional body composition were observed, total body composition was only maintained, and suggests the importance of ultrasound measurements to accurate depict changes in body composition for this population. However, given that this occurred during a period where a loss of lean mass may be likely[10,13] maintenance of lean mass may still be clinically important.

Comparisons to the Literature

The differences between mCRPC and CON from this study illustrate the severity of atrophy that accompanies mCRPC. However, training appeared to partially counteract ADT-related VL muscle loss (Figure 8) and is consistent with previous work done in less progressive

stages of disease[9,15,25,37,39,40,104]. While Hanson et. al (2013)[39] showed regional hypertrophy (thigh muscle volume) in localized PCa survivors on ADT, the current trial demonstrated similar outcomes in more advanced disease with a less vigorous and more convenient model of training. Additionally, 3 months of supervised exercise for PCa subjects with bone metastases undergoing ADT increased physical function[37]. Subjects from Galvão (2018) had only been prescribed ADT for a relatively short period of time (median 2 months, IQR (1.0-6.3)), whereas participants from the current study were 1) clinically diagnosed with more progressive disease (mCRPC) and 2) chronically prescribed primary ADT (average 36 months, standard deviation (33); Table 2). Time on ADT significantly impacts physical function [10,105] and would suggest that the sample used for the current study was arguably more compromised. Nevertheless, physical function appears to have been maintained, which is potentially promising in mCRPC, although needs to be confirmed using non-exercising controls.

Exercise adherence likely plays a critical role in mediating the beneficial adaptations that occurred from this study. Overall, there was a 12.6% increase in VL CSA of (n=14, p=0.012, Cohen's *d*= 0.32; Figure 8). However, when only individuals with an adherence threshold of 70% or greater were analyzed, relative muscle hypertrophy were more than twice as great (26.8%, n=9, p<0.01, Cohen's *d* = 0.70; Table 6). The large difference of effect size between the two groups suggests that higher exercise frequency may be important in a home-based approach, perhaps due to training stimuli that are likely less intense relative to supervised exercise training. Additionally, 40% of the men who completed this intervention did not meet our adherence threshold, this is an area to be targeted in future investigations.

One possible explanation for the lower adherence may be due to the difficulty of certain individual exercises, as there were RT exercises that yielded adherence thresholds of less than

50%, including all the floor-based core exercises and push-ups. Given the age and mobility limitations of our subjects, this low adherence is not surprising but illustrates a need for alternative core exercises in future interventions. On the contrary, all other exercises generated adherence rates of at least 60% and were not statistically different than the 75% adherence threshold established at the start of the study (Figure 7). In addition, increased exercise frequency (and volume) also may have influenced adherence rates, with the lowest adherence rates at week 5 for walking (71%) and week 10 for RT (52%) (Figure 5). For example, at week 5 the walking sessions increase from three to four times a week, perhaps indicating that they may have difficulty adjusting to the greater exercise frequency or that a potential volume threshold may exist. Future studies should look to implore motivational tactics (including appropriate theoretical behavioral models) to help account for weeks with increased exercise frequency or intensity such that participants continue to reap greater benefits through the use of a progressive exercise program.

Implications

Results from this study suggest that exercise can potentially benefit this population. However, the impact is unclear without the use of a control group and demonstrates a need for randomized control trials to determine the efficacy of exercising training during mCRPC. Unsurprisingly, additional benefits appear to occur with greater adherence to the program (Table 6; d=0.70), and emphasizes the importance of increased exercise frequency. Future work should consider methodology that would incorporates a control group, as well as utilizing strategies to help increase adherence. Hybrid exercise interventions that use telemedicine are a viable option, in which exercise professionals would virtually supervise home-based exercise sessions. Participants can potentially exercise in the comfort of their home, while simultaneously

exercising with a trained and qualified individual in the field. Ultimately, this would help to conquer many physical activity barriers and would hopefully provide greater adherence levels for home-based exercise in this population.

Conclusions

Exercise has previously been shown to counteract the consequences of ADT, but men with more progressive PCa, specifically mCRPC, are understudied. The purpose of this study was to examine changes to muscle CSA and MQ in men with mCRPC undergoing ADT, how changes correlated with physical function, and how they compare with age- and BMI-matched controls. Results indicated that this population suffers from extremely low regional muscle mass compared to CON, but that home-based exercise training induces hypertrophy that helps to alleviate the deficit. However, regional hypertrophy was not associated with changes in physical function. Although an apparent exercise threshold was indicated, men who exceeded this threshold experienced effects more than 2x greater of those who did not. The home-based exercise intervention should be improved upon for future studies, and researchers should consider the use of hybrid exercise interventions that utilize technology.

APPENDIX A: WEEKLY FOLLOW-UP FORM

Weekly Follow-Up Form

Participant: (subject #)

Date, Week of Intervention:

Exercise Information (Day, Time):

APPENDIX B: GARMIN SMARTWATCH INSTALLATION INSTRUCTIONS

Garmin Data Extraction Instructions:

1. Log in to Garmin Connect account.
2. Go to “Daily Summary.”
3. Record times in which session criteria are met.

Session Criteria:

1. Elevated heart rate combined with increase in step count
2. Elevations in heart rate and step count must be sustained for at least half of the duration of a walking session for the appropriate week of the program

APPENDIX C: GARMIN SMARTWATCH EXTRACTION INSTRUCTIONS

Exercise log extraction instructions:

1. Call the subject beforehand to ensure that they bring the appropriate test materials before post-intervention testing
2. Once the log has been obtained, confirm that the subject has filled the log out appropriately. Kindly ask the subject about any misconceptions in the log.
3. Once the research team member has confirmed that the log has been appropriately filled out, count the number of RT and walking sessions completed on a weekly basis. Only count the day as a session if at least 75% of the prescribed exercise has been completed
4. If a particular RT exercise was NOT completed, specify in the data.
5. If the subject completed *some* RT exercises but not enough to satisfy an entire session, specify which exercises were completed for individual exercise retention purposes.

APPENDIX D: GARMIN SMARTWATCH SETUP INSTRUCTIONS

Garmin Account Setup Procedure:

1) Create a gmail account.
    - Go to https://accounts.google.com/SignUp?hl=en and fill in the information
    - We have been using uncexss0xx@gmail.com where "xx" is the subject number.
    - It is not important to have the participant's information correct for the gmail account, as only we will access it and it will not affect the data in any way.
2) Create a Garmin Connect account that is tied to that gmail account.
    - Go to https://connect.garmin.com/en-US/signin and click "create one"
    - Create an account using the gmail address that you just created. Agree to the terms and conditions and click "create account."
    - Select "activity tracking" and "fitness" to display on the dashboard.
    - Go to "account settings" and update their "user settings" to give them an accurate height and weight whenever these are known
3) Sync the watch to the new Garmin account.
    - Download Garmin Express: https://www.garmin.com/en-US/software/express
    - Open Garmin Express once it is finished downloading
    - Open the watch from the box. Turn it on and set the appropriate time and date; do not connect with Bluetooth. Connect the watch to the charging cable and plug USB end of the cable into your computer.

- On your computer in the Garmin Express app, click “add device.” Allow the computer to search for and find the watch, and click “add device.”
- Register the watch using the gmail address used to make the Garmin Connect account. Follow prompts on screen. The watch will now be connected to the Garmin Connect Account that you created.
- Go to Garmin Connect https://connect.garmin.com/en-US/signin and sign in using the account information you used earlier. In the upper right hand corner, click the watch icon. It should now say “vivosmart HR” (or whatever you nicknamed the watch if you did so). This website is where their information will be available whenever they sync the watch to their account.
- Update the watch if necessary.

4) Ensure participant is syncing to correct account on baseline testing day
   - They can use either Garmin Connect their smartphone or Garmin Express on their computer.
   - If they use their phone, download the Garmin Connect app. Sign them in using the account information associated with the watch they are being given. Make sure Bluetooth is turned on. On the watch, click the menu button on the side of the watch, and scroll to the Bluetooth icon. Press “pair smartphone.” On their phone, click “add device.” Complete the sync process, and data will periodically sync as long as the Bluetooth connection is maintained.

- If they elect to use their computer, they will need to download Garmin Express on their computer and add the device in the same way as described above. The watch will already be registered to the appropriate account, so they will stop after clicking "add device." The participant will need to periodically connect the charging cable into the computer and open the Garmin Express App. In the app, they can click on the picture of their watch, and then press "sync." The data will sync and be available on Garmin Connect.

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